FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
Hilton Hotel, Washington DC/Silver Spring, Maryland
November 2, 2011

Draft Discussion Points and Questions to the Committee

1. In the Study of Heart and Renal Protection (SHARP) trial, after a median follow-up of 4.9 years, 639 (15.2%) of 4193 Vytorin (10 mg ezetimibe/20 mg simvastatin)-treated patients and 749 (17.9%) of 4191 placebo-treated patients had a major vascular event (MVE), defined as cardiac death, myocardial infarction, any stroke, or revascularization (excluding dialysis access-related procedures); risk ratio of 0.84 (0.75, 0.93), 95% confidence interval (CI), log-rank p=0.001.

The risk ratios for the individual components of the primary composite endpoint are shown in the following table.

	Vytorin 10/20 N=4193	Placebo N=4191	Risk Ratio (95% CI)	p-value
MVE	639 (15.2%)	749 (17.9%)	0.84 (0.75, 0.93)	0.001
Cardiac death	235 (5.6%)	249 (5.9%)	0.94 (0.79, 1.13)	0.51
Non-fatal MI	128 (3.1%)	147 (3.5%)	0.86 (0.68, 1.10)	0.22
Any Stroke	148 (3.5%)	192 (4.6%)	0.77 (0.62, 0.95)	0.02
Revascularization	261 (6.2%)	327 (7.8%)	0.79 (0.67, 0.92)	0.004

In a subgroup analysis by baseline dialysis status, the risk ratio for MVE in the Vytorin 10/20 mg group versus the placebo group was 0.77 (0.67, 0.88) in pre-dialysis patients, and the risk ratio in the Vytorin 10/20 mg group versus the placebo group was 0.94 (0.80, 1.11) in dialysis patients. The interaction p-value was 0.07.

Provide your interpretation of:

a. the primary efficacy result for MVE
b. the treatment effects for the individual components of the MVE endpoint
c. the pre-dialysis versus dialysis subgroup result for MVE

2. Discuss whether you believe that the lack of lipid inclusion criteria in SHARP (e.g., low-density lipoprotein cholesterol [LDL-C]) was appropriate.

3. The standard accepted definition of chronic kidney disease (CKD), according to National Kidney Foundation guidelines, is evidence of kidney damage (including proteinuria) or glomerular filtration rate (GFR) <60 mL/min/1.73m^2 for $\geq$ 3 months. The inclusion criteria for SHARP were age > 40 years and a) pre-dialysis: plasma or serum creatinine $\geq$150µmol/L ($\geq$1.7 mg/dL) in men or $\geq$130µmol/L ($\geq$1.5 mg/dL) in women, as measured at the most recent routine clinic visit AND at the SHARP screening visit or b) on dialysis (hemo or peritoneal).

Draft Discussion Points and Questions to the Committee (*cont.*)

These criteria led to approximately 94% of pre-dialysis SHARP participants having an estimated GFR <45 mL/min/1.73m^2. According to estimates based on the National Health and Nutrition Examination Survey (NHANES), individuals with an estimated GFR <45 mL/min/1.73m^2 represent 15% of the entire CKD population in the United States.

Discuss whether you believe that the criteria used for enrollment of pre-dialysis patients into SHARP provided an appropriate study population to generalize the results from SHARP to the population of all patients with pre-dialysis chronic kidney disease.

4. Provide your interpretation of the safety data from the SHARP trial, in particular, the findings related to muscle, liver, and cancer.

5. Do the available efficacy and safety data provide substantial evidence to support approval of Vytorin 10/20 mg for the prevention of major vascular events in patients with:

a. pre-dialysis chronic kidney disease?

Vote: (**Yes/No**)

b. end-stage renal disease receiving dialysis?

Vote: (**Yes/No**)

Please provide your rationale for each of the above vote.